American Journal of Hematology 61:62–65 (1999)

Sebastian Syndrome: Case Report and Review of the Literature

Guy Young,[1]* Naomi L.C. Luban,[1] and James G. White[2]

[1]Department of Hematology/Oncology, Children's National Medical Center, Department of Pediatrics, George Washington University, Washington, D.C.

[2]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota

Macrothromboctyopenias (MTCP) are a heterogeneous group of disorders associated with thrombocytopenia and giant platelets, and may include other clinical or laboratory findings such as hereditary nephritis, sensorineural deafness, leukocyte inclusions, and cataracts. Patients with MTCP may have mild to moderate bleeding symptoms or be completely asymptomatic. The most recently described MTCP is the Sebastian syndrome (SS), which consists of thrombocytopenia with giant platelets and leukocyte inclusions. Only three previous reports about this syndrome have been published. Herein, we report the first African-American family with SS. The propositus is a 4-week-old male born to a mother carrying the diagnosis of chronic idiopathic thrombocytopenia purpura (ITP). His 4-year-old brother also has thrombocytopenia. There is no history of bleeding symptoms in any of the family members. The diagnosis was established by demonstrating thrombocytopenia with giant platelets and leukocyte inclusions on both peripheral smear and by electron microscopy. This report illustrates the importance of obtaining a family history when evaluating thrombocytopenia with special emphasis on a history of thrombocytopenia, renal disease, deafness, and cataracts. It is important to differentiate between MTCP and chronic ITP to avoid the unnecessary diagnostic studies, and, more critically, unneeded and potentially harmful therapy. Am. J. Hematol. 61:62–65, 1999.

Key words: Sebastian syndrome; giant platelet disorders; macrothrombocytopenia

INTRODUCTION

Macrothrombocytopenias (MTCP) are a heterogeneous group of disorders associated with thrombocytopenia and giant platelets, and may include either all or some of the following clinical features: hereditary nephritis, sensorineural deafness, cataracts, and leukocyte inclusions (Table I). The bleeding symptoms in patients with MTCP are variable and range from moderate mucocutaneous bleeding to no bleeding symptoms, even following hemostatic stress. Most patients do not require therapeutic intervention. May-Hegglin anomaly was the first MTCP reported, and is associated with spindle-shaped leukocyte inclusions [1]. In 1972, Epstein described two families with thrombocytopenia and giant platelets together with features of Alport's syndrome [2] including, sensorineural hearing loss and nephritis inherited in an autosomally dominant fashion [3]. Several other reports of this association were published subsequently [4–6]. In 1985, Fechtner syndrome, a disorder consisting of the above features with the addition of leukocyte inclusions and cataracts was described in a family in which 8 of 17 members were affected [7]. The renal failure and hearing loss associated with Fechtner syndrome usually do not occur until the third to fourth decade as observed also in Alport's syndrome [2]. Subsequently, two reports of MTCP with sensorineural hearing loss but without nephritis have also been reported [8,9].

Sebastian syndrome (SS), first described in 1990 by Greinacher et al. [10], consists of thrombocytopenia with giant platelets and leukocyte inclusions similar to those in the Fechtner syndrome, but without evidence of sen-

*Correspondence to: Guy Young, M.D., Department of Pediatrics, Division of Hematology/Oncology, University of Maryland Medical Center, 22 S. Greene Street, Room N5E16, Baltimore, MD 21201. E-mail: gyoung@peds.umaryland.edu

Received for publication 10 June 1998; Accepted 6 January 1999

TABLE I. Clinical Observations of MTCP Syndromes*

	Platelet number	Platelet size	Leukocyte inclusions	Inheritance	Associations	Reference
Epstein	Decreased	Increased	No	AD	Nephritis Hearing loss	1,2,3,4
Fechtner	Decreased	Increased	Yes	AD	Nephritis Hearing loss Cataracts	5
Sebastian	Decreased	Increased	Yes	AD	None	9,11,12
MTCP (no eponym)	Decreased	Increased	No	?	Hearing loss	6,7

*MTCP, macrothrombocytopenia.

sorineural hearing loss and hereditary nephritis (Alport's syndrome). The leukocyte inclusions are distinguished from the May-Hegglin anomaly in that they are generally more round, and do not contain longitudinally arranged filaments [11]. In platelet aggregation studies, platelets respond normally to all agonists. They demonstrate increased amounts of platelet ATP and ADP likely because of their large size and increased numbers of dense bodies [10]. Only two additional reports of SS have been published, one in a 60-year-old man from Saudi Arabia without bleeding symptoms [12] and another in two members of a family from Spain in whom the mother had a mild bleeding diathesis [13]. In this report, we describe the first African-American family with SS.

CASE HISTORIES

The propositus was a 27-day-old African-American male born to a 26-year-old mother who was gravida 6, para 1 (four elective terminations of pregnancy) and who carried the diagnosis of chronic idiopathic thrombocytopenia purpura (ITP). Delivery was by the vaginal route, uncomplicated, and without excessive bleeding. The mother's platelet count was 10×10^9/l at the time of delivery and $10–20 \times 10^9$/l throughout the pregnancy. She received no platelet transfusions or platelet-enhancing therapy during pregnancy or at the time of delivery. After the birth, there was no evidence of bleeding, ecchymoses, or petechiae in either the mother or her baby. A complete blood count (CBC) was performed on the first day of life which revealed the presence of thrombocytopenia (platelet count of 41×10^9/l). The rest of the CBC was within normal limits. A head ultrasound demonstrated no hemorrhage. The baby had daily platelet counts until discharge; the counts ranged from $41–64 \times 10^9$/l.

The mother of the propositus carried the diagnosis of refractory chronic ITP since childhood, without any significant bleeding manifestations. Her platelet counts range between $10–20 \times 10^9$/l. Previous pregnancies were uneventful and resulted in no excessive bleeding. She gave no history suggestive of menorrhagia, deep tissue bleeding, bleeding with dental procedures or easy bruisability. She had received treatment during childhood and adolescence including steroids and intravenous immunoglobulin (IVIG) on various occasions with no improvement in her platelet count.

The brother of the propositus is in good health and has never had any bleeding manifestations. He was noted on routine CBC to have a platelet count of 90×10^9/l; however he was not evaluated further.

Family history of four generations failed to provide any evidence of hearing loss, nephritis, cataracts, or renal failure.

METHODS

The propositus as well as his mother and brother were evaluated with a complete physical exam including visual fields, fundoscopy, and testing of gross hearing, CBC, and platelet and leukocyte ultrastructural studies. CBC including platelet count and mean platelet volume was performed on a Coulter S plus IV (Coulter Electronics, Ins., Hialeah, FL). Peripheral smears were stained with Wright-Giemsa stain. Platelet and leukocyte ultrastructural morphology was performed as described previously by White [14]. Briefly, platelet rich plasma and buffy coats were suspended in an equal volume of 0.1% glutaraldehyde in White's saline solution for 15 min. The samples were centrifuged, and 3% glutaraldehyde in the same buffer was added to the pellets. The pellets were resuspended and maintained in 4°C for 30 min, and then centrifuged. The supernatant was removed, and the samples resuspended in 1% osmic acid for 1 hr at 4°C. The samples were then dehydrated in a graded series of alcohol and embedded in Epon 812. Thin sections were cut with an ultramicrotome, stained with uranyl acetate and lead citrate, and examined in a Philips 301 electron microscope (Philips Electronics, Mahwah, NJ).

RESULTS

The three patients had significant thrombocytopenia with modest elevations in the mean platelet volume

TABLE II. Clinical Data

	Platelet count	MPV	Leukocyte inclusions	Clinical bleeding
Propositus	62×10^9/l	8.2 fl	Yes	No
Mother	9×10^9/l	8 fl	Yes	No
Brother[a]	14×10^9/l	8.7 fl	Yes	No
	21×10^9/l	10.6 fl	—	—
	25×10^9/l	11.9 fl	—	—

*MPV, mean platelet volume.
[a]The three platelet counts and MPV are from the same specimen with three different gates used to assess platelet number and size.

(MPV) as compared with their age-appropriate controls (Table II). There was no abnormality in the erythrocytes; however, the leukocytes revealed occasional small, round, bluish inclusions. The peripheral smears revealed the presence of giant platelets, many the size of small lymphocytes (Figs. 1 and 2).

Platelet ultrastructural studies revealed the presence of giant platelets that were otherwise normal in appearance in all three family members. There were normal numbers and distribution of alpha granules and dense bodies. The leukocytes demonstrated the presence of inclusions typical of those found in the Fechtner and SS. The inclusions are relatively round in appearance and contain ribosomes and thin filaments (Figs. 3 and 4). The thin filaments and ribosomes are unlike those in the May-Hegglin anomaly as they are not arranged in parallel (Fig. 5).

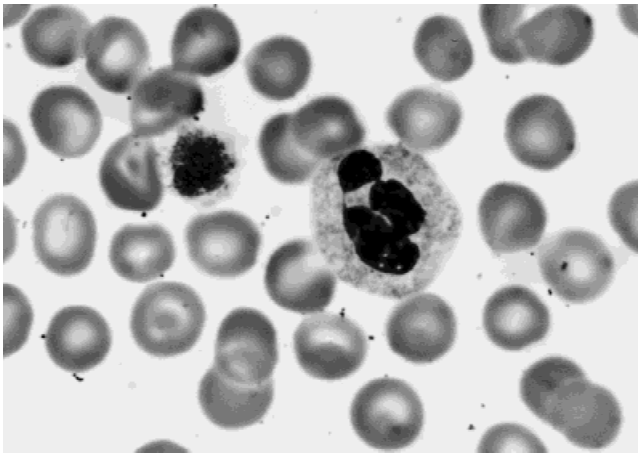

Fig. 1. Peripheral smear photomicrograph with Wright-Giemsa stain of propositus demonstrating giant platelet with an otherwise normal appearance adjacent to a normal neutrophil and normal erythrocytes (magnification, ×1,500).

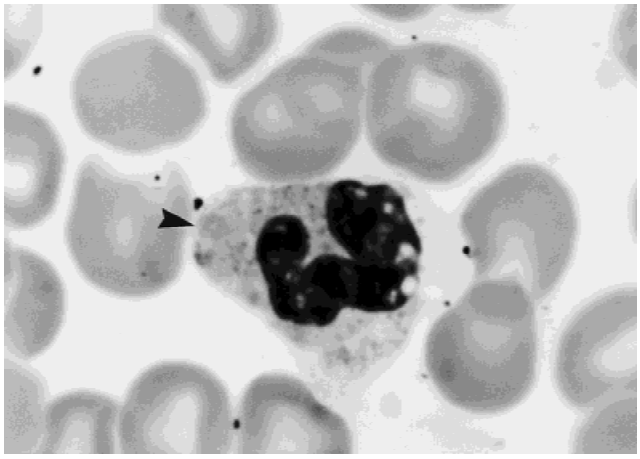

Fig. 2. Peripheral smear photomicrograph with Wright-Giemsa stain of propositus demonstrating a leukocyte with an inclusion (magnification, ×2,000).

DISCUSSION

We report herein the first case of SS in an African-American family. The salient features of this family's case are the misdiagnosis in the mother and initially her infant son, the complete lack of bleeding symptoms despite severe thrombocytopenia, and giant platelets without evidence of deafness or nephritis. The mother carried the diagnosis of chronic ITP since early childhood. Despite an absence of bleeding symptoms, she was treated on numerous occasions with IVIG and prednisone including high-dose prednisone. She elected not to have a splenectomy despite one physician's recommendation. A striking finding in this family is the absence of bleeding symptoms. This most likely is due to the presence of giant platelets. Although, the MPV in this family were only modestly elevated, we believe that the Coulter underestimated both the platelet count and the MPV due to gating of the large platelets with erythrocytes or leukocytes. In fact, the propositus's brother had three different gates used to assess the platelet count. The platelet counts and MPV respectively were 14×10^9/l, 25×10^9/l, 21×10^9/l and 8.7 fl, 11.9 fl, and 10.7 fl. As the gating captured more platelets, the MPV increased indicating that large platelets were not being accounted for. Though the members of this family have thrombocytopenia, their total platelet mass is probably normal, and therefore, they are not functionally thrombocytopenic. Finally, without deafness or nephritis, it is not surprising that the diagnosis of a MTCP was overlooked.

This case illustrates the importance of obtaining a family history when evaluating a child with thrombocytopenia. ITP is the most common cause of childhood thrombocytopenia, and also is associated with the presence of large platelets [15]. Differentiating ITP from the rare MTCP can be difficult. We believe that MTCP may be underdiagnosed, and advocate obtaining an in-depth family history with special emphasis on a history of thrombocytopenia, deafness, nephritis or renal failure when evaluating a child with thrombocytopenia.

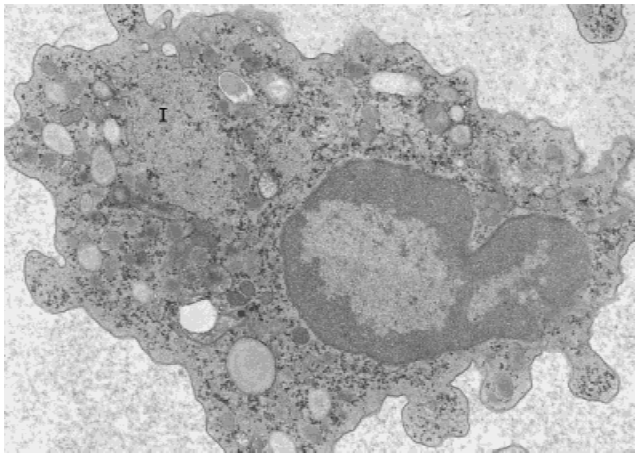

Fig. 3. Thin section electron photomicrograph of a neutrophil revealing an inclusion (I) typical of those found in granulocytes of patients with the SS. The inclusions are not demarcated by enclosing membranes, but do contain small pieces of both rough and smooth endoplasmic reticulum (magnification, ×23,000).

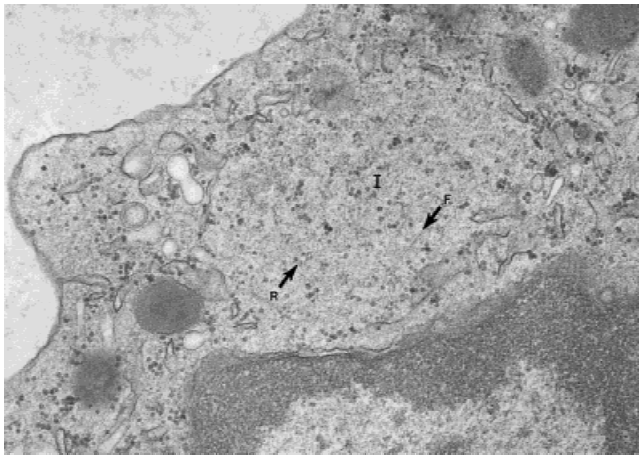

Fig. 4. Thin section electron photomicrograph with higher magnification of a similar inclusion (I) in another neutrophil from the same patient. Bits of smooth and rough endoplasmic reticulum are present, but the inclusion is not enclosed by membrane. Ribosomes (R), smaller and less intensely stained than glycogen particles, and short filaments (F) are dispersed in the matrix of the inclusion (magnification, ×50,000).

CONCLUSIONS

SS is a rare, autosomal dominant disorder resulting in thrombocytopenia with giant platelets, leukocyte inclusions and absence of nephritis, sensorineural hearing loss, and cataracts. This is the first report of SS in an African-American family, and illustrates the fact that these patients do not have significant bleeding problems, and thus must be differentiated from chronic ITP so that they do not receive unnecessary treatments or undergo unnecessary procedures. A family history of thrombocytopenia, deafness, or nephritis should prompt further investigation for MTCP.

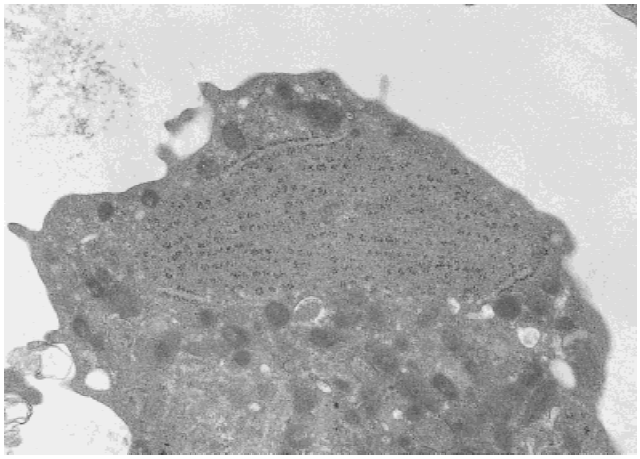

Fig. 5. Thin section electron photomicrograph of a neutrophil from a patient with May-Hegglin anomaly demonstrating the inclusion body which consists of parallel rows of ribosomes interspersed between intermediate filaments (magnification, ×31,000).

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